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Topological Ideas in Stereochemistry

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In commemoration of the centenary of the birth of Lev Aleksandrovich Chugaev

An attempt is made to assemble data for various branches of organic and biological chemistry which can be related directly to the ideas of topology. Consideration is given to problems of topological isomerism and the topological chemical bond, as well as to routes for the synthesis of molecules similar in structure to various geometrical figures. Special attention is paid to catenanes, rotaxanes (hooplanes), and knots. Information is given on the occurrence of topological structures and mechanisms in Nature. A list of 117 references is included.

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1. INTRODUCTION

Stereochemistry examines the spatial relations between atoms and groups within a molecule and also between different molecules. The spatial relations of idealised entities (points, lines, figures) constitute the subject of geometry. Therefore stereochemistry, so long as it is not concerned with dynamic processes, i.e. static stereochemistry, can be regarded as the geometry of molecular entities. That branch of dynamic stereochemistry which is confined to examining processes involving only a change in the internal coordinates of the molecule, conformations—but not chemical reactions—corresponds to introducing the ideas of motion into geometry.

As stereochemistry developed, it became increasingly clear that the relative arrangement of entities was especially important, but, within certain quite wide limits, metrical data (bond lengths, angles) were of little significance. The requirements of configurational stereochemistry are substantially similar to those of topology. This suggests that topology is an adequate mathematical foundation for stereochemistry.

Certain aspects of chemical topology were first discussed in 1961 by Frisch and Wasserman [1]. In a broad sense attention was attracted to topology as a mathematical basis for stereochemistry by a series of articles and papers by the eminent Swiss chemist V. Prelog during 1967–1969 (see e.g. "Problems of Chemical Topology", a lecture given in Dublin on 3rd April 1968 [2]). We shall briefly examine the main stages in the development of stereochemistry from this point of view.

The first step was the formulation of a structural theory, going back to Butlerov (1891). Based on the concept of valency, it established that only n atoms of the total present in the molecule were in a special relationship with a given atom A, where n is the valency of A. Thus the establishment of a topological concept—bond order in general—constituted the essence of the first formulation of a structural theory. The actual arrangement of the atoms—bond lengths and valency angles—is still completely unspecified. In general, nothing prevents directly bound atoms from being further apart than unbound atoms. Only the property of connectedness with respect to A distinguishes these n atoms from the whole set. Hence in the first stage the concept of bonding between atoms is topological rather than chemical.

Let N points belonging to n classes be located in a space (or on a plane, as in the original draft of a structural theory). The valency of a point of the nth class is n, and the number of points of this class a_n, where

$$\sum_n a_n = N.$$

The points may be joined in pairs by a chemical bond without further restriction. This set of points will represent a molecule only if the valency of each point is n (possible variability of valency is ignored for simplicity). The necessary formal condition for the existence of a molecule is $\Sigma n a_n = 2k$, where k is an integer: i.e. the sum of the products should be an even number.

The discovery of optical activity and the isolation of optical isomers, both preceding the development of a structural theory, demanded explanations of the number of structural isomers, which this theory was initially unable to explain. The problem was solved with the emergence of configurational stereochemistry (1875). The geometry of the immediate environment of a given atom—the arrangement solely of the directly bound n atoms (for carbon $n = 4$)—was specified in the tetrahedral model. In this well known history the difference between the van't

Hoff and Le Bel models is interesting for the purposes of this Review. Significantly, it is immaterial for configurational stereochemistry whether the valence tetrahedron of carbon is regular (van't Hoff) or irregular (Le Bel). Strictly speaking, the tetrahedron is always irregular if the substituents are different. A typical feature of stereochemistry—the neglect of metrical relations—is clearly apparent here. The valence angles of the tetrahedron can vary within very wide, though fully determinable, limits without change in configuration. A limit is reached when a coplanar arrangement of the substituents is achieved, when the system becomes achiral†. It is noteworthy that disregard of the metrical aspect of relations between entities is characteristic of topology.

It is appropriate here to define the most important stereochemical concept, configuration. In the Reviewer's opinion an adequate definition is lacking, at least in Russian-language textbooks. The following formulation may be suggested: *the configuration of a fragment is the short-range arrangement of the atoms, which is invariant with respect to the operation of rotation about single bonds*. The absence of superfluous detail enables systems possessing central and other types of chirality to be covered by this formulation.

The van't Hoff–Le Bel tetrahedral model played a decisive part in the practical development of stereochemistry, although the detailed geometry was in some sense a retrograde step in comparison with Pasteur's general ideas on molecular asymmetry as the cause of optical activity.

A direct development of the van't Hoff–Le Bel approach was Werner's coordination theory, which was based on the octahedron ($n = 6$). The success of this theory, which brought harmony into the previously chaotic world of complex compounds, was the first evidence of the universality of stereochemistry, rapidly extending beyond the limits of organic chemistry. When experimental workers came to study compounds of elements in higher periods, they encountered structures in which coordination numbers other than 4 and 6 were realised.

A trend became established to synthesise new molecules corresponding to well known geometrical figures. The progress made in this direction will be examined in Section 2. Subsequent Sections will be concerned with molecular entities for which the concept of topological isomerism is significant, together with their real analogues (catenanes–rotaxanes, isomers of clathrate type connected with the concepts of "inside" and "outside", etc.).

The examination of topological structures is not only intrinsically of great cognitive interest, in the sense of the opportunities for realising mathematical entities in a material, molecular form (where will the limits be reached?). It is no less significant that the actual properties of molecular systems may cause behaviour which is topologically indeterminate but nevertheless almost the same as for a topologically ideal system. This appreciably broadens the range of application of topological ideas and concepts. The clearest example is provided by rotaxanes (see later). While being a combination of cyclic and acyclic molecules mutually arrange in a definite fashion, they behave in effect as catenanes, since the very great steric hindrance makes destruction of this combination impossible without breaking a chemical bond. A less strict analogy to the "atom in cage" topological type is found in clathrates, in particular the subtype of compounds which could be termed "conformational clathrates". Each Section will consider both ideal topological entities and their real analogues.

Several important questions are completely ignored in the Review–the formal concept of Möbius cyclic π-electron systems first formulated by Heilbronner [7] and developed by Zimmerman [8,9] especially in relation to organic photochemistry, topological aspects of aromaticity [10], the systematic formalisation of stereochemistry in terms of topology developed in a series of papers on "Chemistry and Logical Structures" by Ugi et al. [11] on the basis of the concepts of Bourbaki's French school of mathematics.

2. REALISATION IN CHEMICAL MATERIAL OF RIGID THREE-DIMENSIONAL STRUCTURES NOT REQUIRING THE CONCEPT OF TOPOLOGICAL ISOMERISM

During recent years several authors [12–16] have discussed the problem of the polyhedra corresponding to various coordination numbers and the rearrangements of ligands occurring in such systems ("polytopic rearrangements"). A fundamental mathematical condition here is Euler's theorem—the first theorem of topology—according to which $V + F = E + 2$, where V, F, and E are the numbers respectively of vertices, faces, and edges.

There exist five regular convex polyhedra—tetrahedron, cube, octahedron, dodecahedron, and icosahedron—whose faces are respectively triangles, rectangles (squares), triangles, regular pentagons, and triangles. With the exception of the dodecahedron, they are all represented in molecular structures. Unsubstituted cubane was synthesised in 1964, [17] and its chemistry has since been developed considerably. Published data on simple derivatives of tetrahedrane are contradictory [18–20]. However, the existence of the tetrahedral ligand P_4 has been proved in complexes of platinum-group metals [21]. Several types of octahedral molecules are known, besides complexes of metals having coordination number 6, corresponding to a centred octahedron. The purely carbon octahedrane, which would have represented a C_6 molecule, is merely a fragment of the diamond lattice. Nevertheless, the octahedral molecule $C_2B_4H_6$ is known [22]. Carboranes-12, having the form of an icosahedron, have been widely studied‡.

In 1964 Woodward et al. [24] synthesised the unsaturated hydrocarbon triquinacene $C_{10}H_{10}$, which forms, as it were, half a dodecahedral molecule



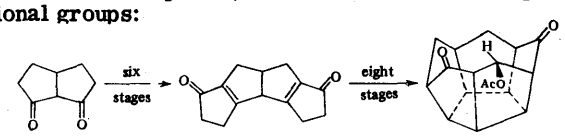
and may be a convenient precursor thereof. The same paper [24] reported the intention of subsequently studying the behaviour of triquinacene as an olefinic ligand in metal complexes, but further communications have not followed. However, such complex formation would have opened up prospects for dimerisation and also for obtaining compounds of "caged atom" type.

A different route for synthesising dodecahedrane, from two subunits—C_5 cyclopentane and a C_{15} fragment termed "peristylane"—has been chosen by Eaton and Mueller [25].

†Estimation of the energy required to convert tetrahedral into planar carbon shows that it exceeds the dissociation energy of the carbon–carbon bond [3]. The possibility of achieving a planar configuration of carbon has been examined by Hoffmann et al. [4,5], who have also discussed the possible stabilisation of a trigonal pyramid [6]

‡A review has appeared [23] on polyhedral organic molecules.

Starting from *cis*-bicyclo[3,3,0]octane-2,8-dione, they obtained the chosen peristylane derivative containing three functional groups:



(the structural similarity between peristylanes and [5]circulenes is obvious—see later). No information was given on the further plan of synthesis. High thermal stability was predicted[12] for dodecahedrane, with a stable carbanion consequent on effective delocalisation of the charge over the surface.

The requirement that the quadrivalency of carbon should be maintained probably makes the existence of a purely carbon icosahedron impossible. According to Euler's theorem this figure has 20 faces and 30 edges, with 5 edges meeting at each vertex, which implies that every atom is directly bound to at least 5 neighbours. Because of the variation in the type of bond this geometry becomes possible for carboranes $C_2B_{10}H_{12}$, in which all the atoms, including the carbon atoms, are formally six-coordinate. One valence is directed towards a group situated outside the ring system. However, $MC_2B_9H_{11}$ systems have been obtained in which the metal atom is unsubstituted[26,27]; derivatives of lower carboranes with an unsubstituted carbon atom have also been prepared[28]. The diversity of carborane structures is probably far from exhausted. The possibility of realising rigid non-convex polyhedra is of great interest from the point of view of structural topology. There are certainly no formal prohibitions of their existence with a sufficiently large number of vertices, and the availability of experimental methods for partly breaking down the structure of polyhedra (e.g. by removing one boron atom) may pave the way to the preparation of rigid non-convex polyhedra.

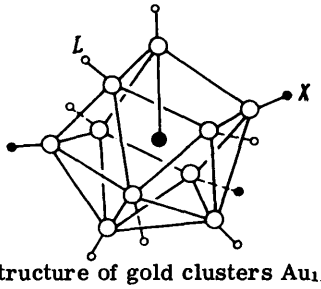
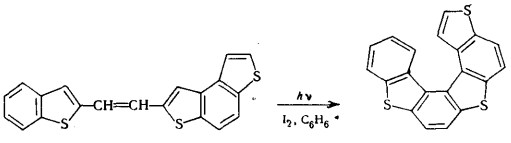


Figure 1. Structure of gold clusters $Au_{11}L_7X_3$ (where L = triphenylphosphine, and X is an anionic group).

Clusters form a special group of organometallic compounds, whose chemistry has been developed only during the past decade[29]. These molecules contain closed systems of metal atoms (usually of a single metal). At first only planar clusters were known, but now three-dimensional clusters have also been obtained, whose structure has been established by X-ray examination. Gold clusters have been studied fairly thoroughly, e.g. $Au_{11}L_7X_3$,[30-32] which has been interpreted as a centred icosahedron in which the site of three vertices is occupied by a single atom (Fig. 1). Another example of a metal cluster will be considered later in connection with "atom in cage" isomerism. Although ideas on the nature of the bond between the metal atoms in clusters are still fairly vague, there is no doubt about the existence of this bond, covering the whole cluster system, as is indicated in particular by the close similarity of all distances between metal atoms, including the internal atoms.

A clear example of the realisation of three-dimensional geometrical models is provided by the helicenes—molecules having the form of a fragment of an infinite screw surface—the first and for a long time the only representative of which, hexahelicene, was prepared and resolved into optical enantiomers by the brilliant work of Newman and his coworkers[33-35]. A characteristic property of this molecule—optical activity due to the presence of an actually asymmetric chromophore, which reflects the chirality of the screw surface—immediately attracted the attention both of theoreticians and of experimentalists. However, the investigations were complicated by the difficult accessibility of the compounds. Theoretical calculations of the absolute configuration of hexahelicene by different methods[36-41] gave discordant results.

More rapid progress has been made with heterohelicenes, mainly containing one or more thiophen rings, which have proved especially suitable for the necessary synthetic procedures. This route



has been developed in the laboratory of the Dutch chemist Wynberg[42-45]. In the course of this work the absolute configuration of a molecule of helicene type, [*d*]naphtho-[1,2-*d'*]benzo[1,2*b* : 4,3-*b'*]dithiophen, has been determined for the first time[44] from the anomalous dispersion. The same method has recently been used to establish the absolute configuration of 2-bromohexahelicene, which has been converted into hexahelicene[46,47]. With all three molecules the (−)-enantiomer forms a left-hand spiral, with absolute configuration M (Fig. 2). Thus the problem of hexahelicene, posed fifteen years ago, has been solved.

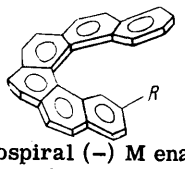
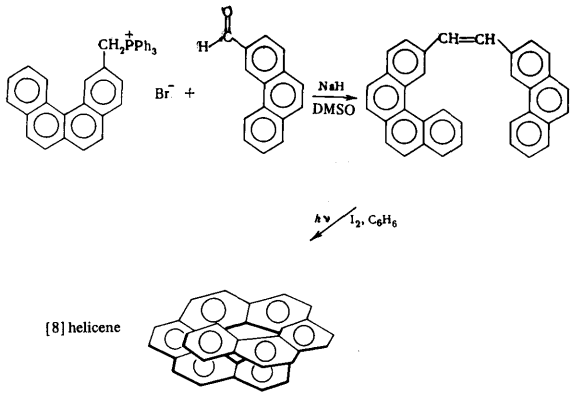


Figure 2. Laevospiral (−) M enantiomer of hexahelicene and 2-bromohexahelicene (R = H, Br).

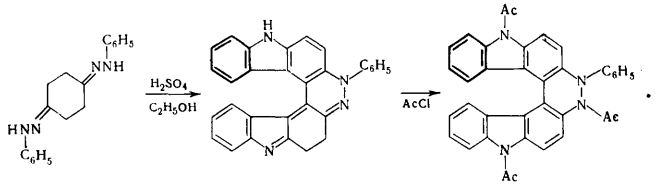
Martin et al.[48-50] have achieved considerable synthetic success in developing a new route to helicenes based on

the oxidative photocyclisation of 1,2-diarylethylenes:

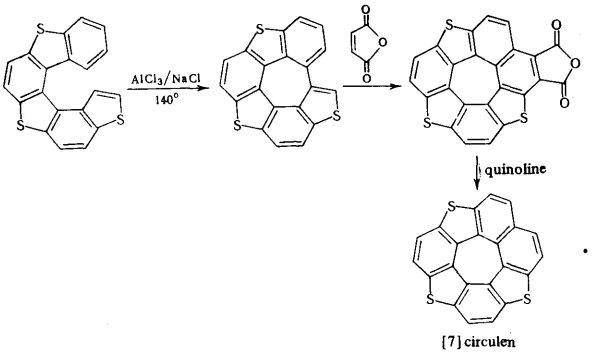


This method has already yielded homologous helicenes right up to [13]helicene, which consists of two turns of a screw surface.

It is interesting that the higher helicenes are spontaneously resolved into enantiomers on crystallisation. A good method for the optical resolution of helicenes is to crystallise them from an optically active solvent. Steric hindrance in these molecules is obviously so great that the packing together of molecules of different configurations in the same crystal becomes disadvantageous. Spontaneous resolution into enantiomers had previously been observed extremely rarely [51]. Azahelicenes have also been obtained in optically active form by a different method [52]:

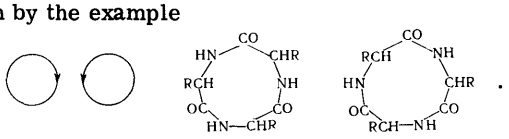


An interesting type of molecule is a circulene, a general name given by Dopper and Wynberg [53] to molecules comprising aromatic or similar rings fused on each side of a polygon. These workers examined cases in which the number of sides was n = 5–7. With a hexagon the planar aromatic molecule coronene, already known for quite a long time [54], is obtained. With n = 5 an example of a [5]circulene is corannulene [55]. The resulting stress forces the molecule out of a plane, making it buckle into a bowl shape. There is an obvious structural relation between [5]circulenes and peristylane, hetero-substituted derivatives of which can be obtained by further hydrogenation of hetero[5]circulenes. The first synthesis has been reported [53] of [7]circulenes, which should have a folded, corrugated form. In this case the perimeter of the molecule is longer than that of the planar coronene, whereas with corannulene the perimeter is shorter than in coronene. A [7]circulene has been obtained both by photocyclisation and from a [6]heterohelicene [53], which establishes a relation between two interesting classes of compounds:



3. TOPOLOGICAL ISOMERISM AND THE TOPOLOGICAL BOND

The widespread representation of molecules as geometrical figures, especially if all the atoms in the chain are identical, is generally used for carbon rings. However, the introduction of other structural entities (substituents, heteroatoms, etc.) leads to an internal orientation of the molecule, in which a definite direction of travel is distinguished. Such structural orientation assimilates a molecule to a path in the topological sense. The importance of structural orientation for stereochemistry is shown by the example



The two circles of the same radius are not congruent when displaced in a plane, if the direction of motion indicated by the arrow is taken into account: they are enantiomorphous if escape from the plane is forbidden. If the circles are replaced by cyclic molecules, an analogous orientation of the ring can be effected by means of different fixed sequences of non-equivalent groups. In *space* the above molecules (cyclotriglycines) can be superimposed as before. The situation is different, however, if the ring contains chiral centres differing in configuration. Combined with the fixed sense of the ring this leads to the appearance of a new type of isomerism, cyclostereoisomerism, which was actually discovered in cyclopeptides and their analogues [56, 57].

A most interesting branch of structural topology relates to information on the preparation and properties of molecules for which the concepts of topological isomerism and topological bonding are essential. Topology considers only those properties of a geometrical configuration which are preserved during deformations not involving rupture of lines and bonds§.

In general, two chemically non-bonded molecules can usually occupy independently any relative positions in space. However, a mutual arrangement is possible such

§Configurational stereochemistry presents more rigorous demands, since it takes into account the difference between enantiomers.

that it is not possible by any continuous transformation to achieve *all* relative positions: a chemical bond must be ruptured. In this case the combination of two species constitutes a new individual though composite molecule, whose integrity is accomplished by a new type of bonding, topological. This composite molecule is a topological isomer of the sum of the two separate component molecules [58]. According to Schill and Zürcher's definition [59] a characteristic feature of compounds having a topological bond is the property¶ that "main valency bonds must be broken in order to separate the complete molecule into its components, although no chemical bond is present between the two moieties".

We shall consider three types of topological isomerism. One depends on the relative arrangement of linear (one-dimensional) entities in space—whether looped or knotted—and is fundamentally impossible on a two-dimensional plane†. It includes catenanes, the first class of topologically bound molecules to be studied. They consist of at least two simple closed curves. Knotted lines are topologically isomeric with one simple closed curve, into which, however, they cannot be transformed without breaking the line.

The second type of topological isomerism is associated with the concepts of "inside" and "outside". It is realised even in a two-dimensional model, as is evident from the example



of topological isomerism in a plane. Chemistry is interested in the three-dimensional case of a "molecule in a cage". This type of topological isomerism, in contrast to catenanes, can be achieved only because atoms are real physical bodies, not geometrical points. The set of spheres formed by the van der Waals radii of chemically non-bonded atoms in a molecule effectively create a closed surface. As a consequence, an atom or a molecule in the inner region‡ is unable to pass into the outer region, since it is of finite size. From a purely chemical point of view a "molecule in a cage" represents an intramolecular analogy to inclusion compounds—clathrates.

Whereas in the first type of topological isomerism entities were represented by two lines, and in the second type by at least one closed surface, open surfaces appear in the third type. It is fairly obvious that segments of cylindrical surfaces can be joined on the catenane principle: this is a trivial analogue of the linear case. It is more interesting that they can be twisted any number of times n. Thus a cylinder ($n = 0$) is topologically isomeric with a Möbius strip ($n = 1$) and with all higher figures having $n > 1$. The upper limit of n is imposed by the width of the strip and the diameter of the cylinder.

¶This definition, which was given for catenanes, is valid for other classes, and also in some measure for analogues, of compounds having a topological bond, e.g. rotaxanes (see later).

†For non-self-intersecting figures.

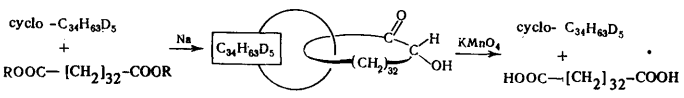
‡It is implied that the enclosing molecule forms a two-sided closed surface, to which Jordan's three-dimensional theorem applies.

4. CATENANES, ROTAXANES, AND KNOTS

Ideas on the synthesis of such molecules, which consist of two entwined rings, i.e. mechanically rather than chemically bound compounds, like links in a chain—hence the name *catenanes*—have been expressed more than once by different scientists, beginning at the latest with Willstätter [1]§. However, experimental work on this problem began only little more than a decade ago. In view of the availability of a review [59] and a monograph [61], of which the latter has been translated into Russian, it appeared advisable to present a somewhat abridged account of the problem of catenanes.

In order that steric hindrance by non-bonded atoms should enable one ring to pass through another, both rings should be large, each containing more than twenty atoms. A prerequisite for such investigations, therefore, was the development of methods for the synthesis of macrocyclic compounds, which was largely accomplished by the 1950s.

Two principles—statistical and directed—are now known for the synthesis of catenanes. In 1960 Wasserman [58, 62] obtained the first reliable evidence for the formation of a catenane, by subjecting the diester $ROOC.[CH_2]_{32}.COOR$ to acyloin condensation in the presence of the partly deuterated cyclic hydrocarbon $C_{34}H_{68}$:



In a random synthesis the probability that a linear molecule will undergo cyclisation at the same time as it has passed through a macrocyclic ring is extremely small. The yield of catenane in this method of synthesis is therefore negligible, and its formation was proved by isotopic labelling and mass spectrometry.

Further work on statistical synthesis used the metathesis of alkenes on catalysts including compounds of transition metals [63]. Wasserman, Ben-Efraim, and Wolovsky [64, 65], using intermediate cycloalkenes and a catalyst comprising tungsten hexachloride, ethylaluminium dichloride, and ethanol, obtained a mixture of cyclic oligomers up to at least C_{120}. Metathesis on transition metals is an intermolecular reaction. With a sufficiently large ring, however, this may be followed by intramolecular reactions. Some of them may yield catenanes, knots ("nectinodanes"), and Möbius strips ("plectanes"), as can be seen from Scheme 1. [65]

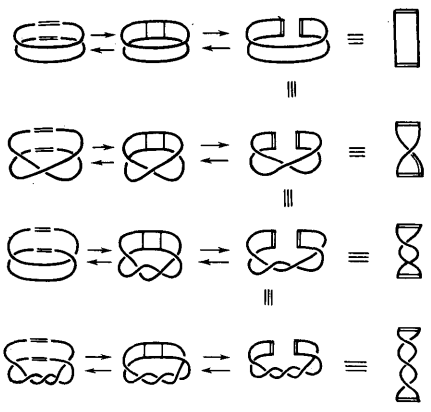
Although a circle can be deformed continuously into the edge of a Möbius strip, the statistical probability of achieving such a conformation is very small. It is another matter if some favourable factor is operating, e.g. coordination of double bonds of the cyclic molecule with a metal. In 1970 Wolovsky [65] and Wasserman et al. [66] published simultaneously very similar results on the metathesis of *cis*-cyclododecene on a tungsten catalyst, which indicated the formation of catenanes. The xylene-soluble fraction of the product was subjected to continuous mass-spectrometric analysis¶ while the temperature was gradually raised. A monotonic increase in the mass

§An interesting essay on these questions appears in Kostyanovskii's booklet [60], directed at the non-specialist reader; some historical information will also be found.

¶Kostyanovskii [67] in 1965 mentioned mass spectrometry as a convenient method for detecting catenanes.

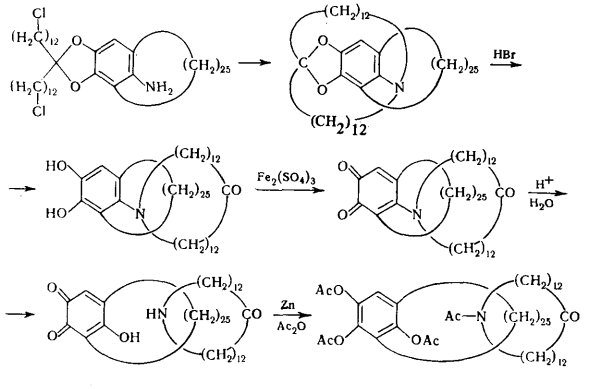
number of the most intense peak was found. At a certain temperature, however, peaks corresponding to lighter masses also showed a sharp increase in intensity. This phenomenon was explained by thermal rupture of the catenanes, the most abundant of which probably comprised C_{72} and C_{84} single rings. If the reason had been irregular cracking of monocyclic hydrocarbons, the mass spectrum would have shown an increase in intensity of a whole group of ions of closely similar mass. These workers adduced other arguments in support of the formation of catenanes (including multicatenanes), which will not be discussed here. It depends on the probability that a macrocyclic ring will buckle in a certain way, and this distinguishes it from Wasserman's first synthesis [58], which was governed by the probability that a chain would pass through a ring. Other aspects of the statistical synthesis of catenanes have been discussed [68, 69].

Scheme 1



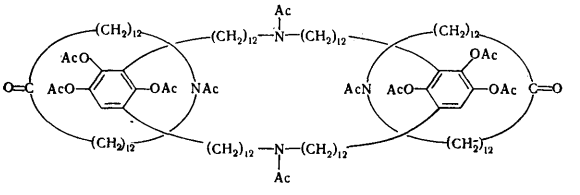
A fundamentally different route was used in the directed synthesis of individual catenanes. Work on this problem began in the laboratory of Lüttringhaus during the 1950s as a development of the synthesis of "ansa" compounds. For a long time the desired result could not be obtained [70]. Success was finally achieved by Schill [71, 72], who synthesised the first [2]catenane by the sequence of reactions in Scheme 2. This synthesis made use of special supports or "scaffolding", by means of which the required groups were retained in a fixed position. They were then selectively removed by procedures which did not affect the remainder of the molecule. As a result it was possible to achieve the synthesis of two interlinked macrocyclic rings joined by a bridge, which was eliminated in later stages.

Scheme 2

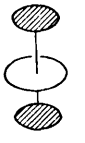


The "scaffolding" method requires great selectivity and great experimental skill. It ensures correct assignment of structure and provides an approach to the synthesis of higher catenanes. The first [3]catenane was obtained by Schill and Zürcher [73] (Scheme 3). The actual working out of a route for a directed synthesis is an extremely difficult task. In practice Schill's group have used the same chemical reactions in all their syntheses of catenanes and rotaxanes.

Scheme 3



Wasserman [58] had previously and with complete justification defined a catenane as a topological isomer of two uncombined cyclic molecules. The molecular nature of the entities, however, leads to the curious situation that, if a linear molecule with bulky groups at its ends (dumbbell-shaped) passes through a macrocyclic ring, the resulting system



behaves analogously to a catenane: its components also cannot be separated without rupture of a chemical bond. Such systems are termed *rotaxanes*†.

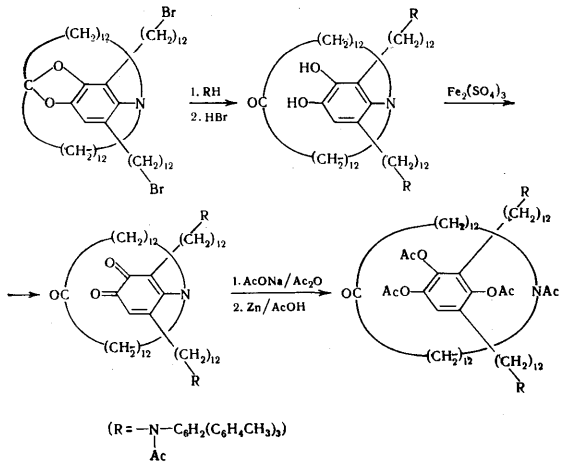
Schill and Zollenkopf's synthesis [74] is shown in Scheme 4. Nevertheless, in contrast to catenanes, rotaxanes are topologically indistinguishable from the simple sum of linear and cyclic molecules. This is shown especially clearly by work on the statistical synthesis of rotaxanes [75, 76]. A macrocyclic C_{30} acyloin was bonded to a polymeric carrier—Merrifield's resin—and subjected to repeated treatments with decane-1,10-diol and triphenylmethyl chloride in a solvent containing pyridine. Mild alkaline hydrolysis was followed by the chromatographic isolation of 6% of a rotaxane, in which either the ring or the linear portion could be broken selectively. Harrison [76] has recently detected extraordinary selectivity with respect to the size of the ring. Simply heating the macrocyclic hydrocarbon with 1,10-bistriphenylmethoxydecane in solution to 120°C leads to *equilibrium* between the rotaxane and the separate components *only for* C_{29}.

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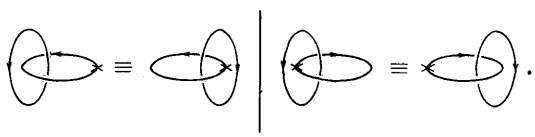
†Inclusion compounds with cyclodextrins are directly relation to rotaxanes (see later).

In the presence of trichloroacetic acid the reversible removal of one triphenylmethyl group makes it possible to obtain rotaxanes with C_{25}–C_{29}. With a larger ring the triphenylmethyl group will obviously pass through freely. The remarkable simplicity of this synthesis of rotaxanes should stimulate further investigations on these lines.

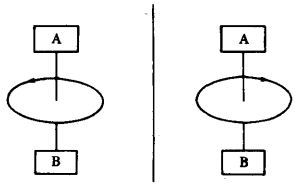
Scheme 4



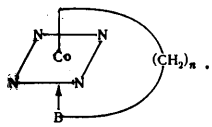
All catenanes and rotaxanes known hitherto have contained at least one ring of symmetrical structure, so that problems of chirality were not directly involved in these systems. If, however, this ring were oriented by unsymmetrically arranged heteroatoms or groups (indicated by an arrow in Scheme 5), the possibility of enantiomerism would arise, as is shown by the rotaxane in Scheme 5. A [2]catenane will likewise be enantiomeric if its two rings are not identical and are oriented:



Scheme 5

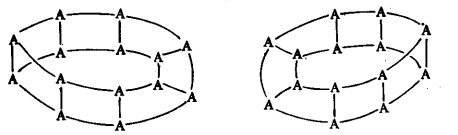


Coordination compounds of metals can be used as "scaffolding" for building up catenoid structures. A system consisting of a metal atom fixed in a planar quadridentate ligand, with the two remaining positions in the coordination octahedron joined by a long chain, would be analogous to a catenane. The best simple example of such a complex, the approach to whose synthesis is self-evident, is an amminepolymethylenecobalt derivative of the type



The macrocycle is completed at the cobalt atom by means of a σ-bond with carbon and a donor-acceptor bond with a basic group B (e.g. phosphine or amine). This structure is formally of the catenane type, but differs in having nitrogen–cobalt coordinate bonds between the two rings.

Catenanes are the only class of topological molecular structures that have yet been synthesised. It would be an extremely interesting problem to construct a molecule having the geometry of a one-sided surface—the Möbius strip

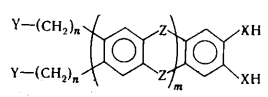


Double cyclisation of a long molecule in the form of a fairly stiff band can be effected two ways—XY, X′Y′ to give a cylinder, and XY′, X′Y a Möbius strip



(cf. scheme of metathesis of cycloalkenes). In this statistical method of synthesis the probability of each mode of cyclisation would be close to 0.5 (in contrast to catenanes).

A suitable model molecule, which can easily undergo conformational flexing, can be constructed by introducing for instance aromatic fragments. Thus the A–A units can conveniently be benzene rings joined by short bridges comprising one or two atoms. These compounds are evidently oligomers (in particular oligoarylates) in size and structural form. For example, the edge of the cylinder for the molecule



will contain $N = 4m + n + 4 = 4(m + 1) + n$ atoms, and the edge of the Möbius strip twice this number. If we assume that $N = 20$, which seems quite reasonable, we have

$m = 1;\ 2;\ 3;\ 4.$
$n = 12;\ 8;\ 4;\ 0.$

It must be borne in mind, however, that the overall rigidity of the system increases with increase in m, owing to the accumulation of aromatic rings, and N should increase. The connecting bridges could be either oxygen atoms or methylene groups.

Another aspect of the problem of the Möbius strip concerns the occurrence of conformational transitions of macrocyclic compounds in solution, not the construction of a rigid molecule. This applies to the case in which the A–A units are interlinked not covalently but by weaker interactions, e.g. of donor–acceptor type. With a suitable arrangement of heteroatoms and functional groups a large ring (having $N \simeq 40$ or more) may assume the conformation of the edge of a Möbius strip.

Finally, it must be noted that the Möbius strip should exist as two enantiomeric forms, and therefore possess inherent optical activity, as a consequence of its property of orientability, even when constructed of identical atoms.

It has been shown above that, as in the metathesis of cycloalkenes, not only catenanes but also knotted molecules ("nectinodanes") and twisted molecules ("plectanes") can be obtained [65,78]. These possibilities follow directly from solving the geometrical problem of cutting a cyclic strip which has been twisted n times. Such molecules have not yet been synthesised. In an early paper Wasserman [62] estimated the minimum number of atoms from which the simplest knot, a trefoil, can be formed as $n \geqslant 50$. The first search for a knotted molecule was then undertaken in the random cyclisation of a C_{66} diester.

A remarkable property of knots is their chirality. Because it has been twisted in a definite direction, a knotted molecule should possess intrinsic optical activity. The optical rotation of the trefoil knot $[CH_2]m$ has been calculated [78] on Kirkwood's theory. With $m = 66$, when interactions of non-bonded atoms produce no appreciable distortions in the structure, the calculation gives $[\alpha]_D = +2.1°$, i.e. $[M]_D = +19.4°$, for the absolute configuration depicted on the left-hand side of



The smallness of the absolute rotation introduces uncertainty into the assignment of configuration, since even slight departures from the ideal structure employed in the calculation may produce a change in sign. Optical activity may be an indication of the formation of knotted molecules in random synthesis [62].

No attempt at directed synthesis has been reported. Scheme 6 suggests a synthesis for a trefoil knot using an octahedral metal complex as matrix.

5. TOPOLOGICAL ISOMERISM CONNECTED WITH THE CONCEPT OF "INSIDE" AND "OUTSIDE"

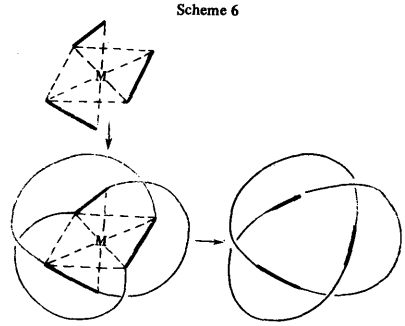
No single example is yet known of purely topological isomerism due to the enclosure of one molecule (or atom) in the space bounded by another molecule, without specific interactions between them. We shall therefore consider here more or less close analogies arising in real systems.

Inclusion compounds or clathrates have long been known [79], in which molecules are located in the cavities of a crystal lattice formed by molecules having a different structure. Clathrates, whose structure was understood more than twenty years ago, are of no special topological interest, since the intermolecular bonds usually are easily broken when the crystalline state is disturbed.

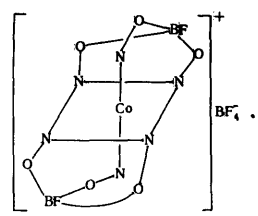
Cases are possible in complicated, conformationally mobile systems where some species may be "trapped" and retained by forces weaker than a covalent bond. An interesting example is the selective bonding of a xenon atom by myoglobin [80], which probably has a clathrate structure. Capture is accomplished in solution or in the crystal by the conformational mobility of the protein molecule. Hydrophobic interactions may play an important part here. Other examples provided by natural compounds will be discussed in the final Section of the Review.

Mention must be made of interesting systems in which isomerism of the "inside–outside" type is effected by a coordinate bond (encapsulation reactions). In 1967 Pedersen [81] discovered the class of cryptates, introducing into practice macrocyclic ligands containing several ethereal oxygen atoms ("crown ethers"). With suitable size and conformational mobility of the ring they form stable complexes with metal ions, mainly of Groups I and II, the selectivity depending on the structure of the ligand. Research on cryptates is developing rapidly [82–84], and analogous principles of complex formation have proved to be of biological importance (see later).

Scheme 6

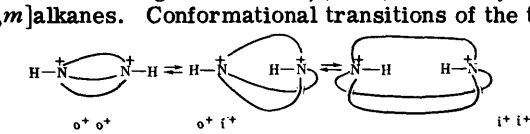


Boston and Rose [85] obtained a kind of clathratochelate containing a cobalt ion



The synthesis is based on the principle of treating an ordinary octahedral complex, having three bidentate ligands, with a reagent capable of "locking" the three ligands located on opposite faces of the octahedron.

In the same year 1968 Park and Simmons [86] studied the isomerism arising in salts of 1, $(k + 2)$-diazabicyclo-$[k,l,m]$alkanes. Conformational transitions of the type

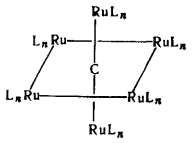


are possible in such macrobicyclic diamines when $k, l, m > > 6$‡. These equilibria have been studied in solutions of various acids by proton magnetic resonance. It is especially remarkable that encapsulation of halide ions occurs when $k = l = m \geqslant 9$. The corresponding isomeric salts, catapinates, are more sparingly soluble and are precipitated from solution. The [9,9,9]diamine will yield $i^+Cl^-i^+[9,9,9]Cl^-$ only after standing at 25°C for five days, the reaction is more difficult with the bromide, and no catapinate is formed at all with the iodide, whereas the [10,10,10]diamine rapidly gives encapsulation products of Cl^-, Br^-, and I^-. Thus the steric requirements of the bicyclic molecule are fairly definite. It is very likely that the anion is retained in the "interior" by two hydrogen bonds.

‡Hydrogen or nitrogen directed outwards is denoted by o^+, and inside the molecule by i^+.

The inclusion compounds of graphite [87,88] form a peculiar class closely resembling clathrates. The occluded molecules are trapped in them by a single macromolecule, which does not in general enclose a portion of space. However, the actual conditions are such that escape of occluded molecules from the space between the layers is in practice difficult (e.g. high temperatures are required). During recent years analogous layer compounds (intercalation complexes) based on niobium and tantalum disulphides and diselenides have been discovered. The occluded molecules may be amines, e.g. pyridine or aniline [89,90]. Hardly any work has yet been done on these complexes, but they are attracting attention in connection with the problem of superconduction.

Several structures are known formally corresponding to the "atom in cage" type. They include the interesting organometallic carbide clusters [91]. The carbon atom situated at the centre of a regular octahedron formed by six ruthenium atoms



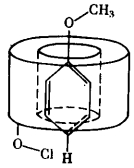
appears to correspond to the topological condition. However, the carbon–ruthenium distances are too small (1.88–2.12 Å), which undoubtedly indicates the presence of a chemical bond.

Organometallic chemistry is in general a suitable field of activity for seeking topological isomerism of the "inside–outside" type. Early attempts were made [92] to synthesise "cage" structures based on metallocenes. This is a practicable approach. An especially useful property of many organometallic compounds is their reducibility to the metal. If a compound is thus obtained in which the metal inside the cage is bound by a chemical bond (σ or π), a reducing attack on this bond can be conducted from outside the molecule, e.g. by electron transfer. However, it is not clear beforehand whether the resulting metal atom is sufficiently inert not to demolish the cage. In any case, the current state of the science allows such a problem to be investigated experimentally.

6. TOPOLOGICAL STRUCTURES AND MECHANISMS IN NATURE

An important factor for naturally occurring molecules, especially for macromolecules with their abundant possibilities of variation in conformation, is the relative arrangement, quite often a prerequisite for chemical interaction. Such systems are of direct interest in connection with the problems under discussion.

Natural complexes of clathrate type were the earliest to become known. Dextrin polysaccharides include cyclodextrins having cylindrical macromolecules. Molecules of a certain size are able to penetrate inside the cylinder [93], and their retention is assisted by hydrophobic interactions. The formation of such inclusion compounds with cyclodextrins or cycloamyloses has been used to resolve certain chiral molecules into enantiomers [94]. Breslow [95,96] has applied the formation of cyclodextrin clathrates to effect a kind of catalysis. If the linear portion of a molecule is placed inside the cylindrical macromolecule of a cyclodextrin, the groups outside (usually inert) are close to the agent and undergo uncharacteristic reactions. In this way it has proved possible to substitute chlorine in anisole solely in the *para*-position by the action of hypochlorous acid



and more rapidly than in the uncomplexed substrate. Breakdown of the clathrate gave a high yield of *p*-chloroanisole [95].

Preliminary clathrate formation has also enabled model esters to be hydrolysed with rate constants comparable with those found in the hydrolysis of esters by esterases [96]. The principle of preliminary favourable orientation of reactant molecules is adopted by enzymes. The high rates of enzymatic reactions are in fact known to be due to the formation of an enzyme—substrate complex, which can in some sense be regarded as a conformational but not a topological isomer of the separate enzyme macromolecule and substrate molecule§.

The great conformational mobility of biological macromolecules and the abundance of functional groups are closely connected with their biological functions. Thus it has been found quite recently [98,99] that the biological activity of peptide antibiotics of the valinomycin type involves the selective formation of simple complexes of cryptate type with alkali-metal ions, and ultimately the transport of these ions across cell membranes.

The formation in Nature's laboratories of extraordinarily complicated and highly specialised molecules suggests the probable occurrence of topological structures and mechanisms. Their identification, of course, involves very great difficulties. In fact, the disruption of the integrity of biological entities during study may change their structure beyond recognition. Nevertheless, clear evidence has now been obtained of the existence of catenoid deoxyribonucleic acids in the mitochondria of several cells, both pathogenic and normal. These first natural catenanes were discovered in 1967 by the American biochemist Vinograd and his coworkers [100,101], who obtained their electron micrographs. Individual macrocycles reached 5 μm. The micrographs clearly revealed also higher linearly linked catenanes up to a [7]catenane. Further work has shown that catenoid DNA are widely distributed.

Schill and Zürcher [59] have suggested a possible mechanism for the biogenesis of catenoid DNA on the basis of known properties of the Möbius strip. The hypothesis that cyclic DNA are constructed on this principle was first put forward some time ago by Wasserman [62]. Eight years later Burdick showed that it would not contradict the known properties of cyclic DNA [102]. If a Möbius strip twisted n time is cut along the midline, catenanes are formed whenever n is an even number; when n is unity, a single ring is obtained with a double circumference; and other odd values of n yield various knots [78]. The replication of double-strand Möbius DNA, which is equivalent to this slitting, thus naturally yields catenoid and knotted macromolecules (the latter have not yet been detected).

§During recent years experimental methods have been developed enabling a detailed study to be made of the character of the effective surface of macromolecules. It is advisable to term such work study of the topography of the surface of the molecule [97]: use of the term "topology" in these cases is incorrect.

In view of the probable existence in Nature of molecules simulated by one-sided surfaces like the Möbius strip, the existence of closed one-sided surfaces does not appear improbable. In three-dimensional space such surfaces can be realised only with self-intersection: i.e. the three-dimensional Jordan theorem is not applicable to them, and they do not divide space into internal and external regions.

The postulated possible existence of structures having such properties is directly related to the problem of membrane transport. The proposed topological hypothesis makes no demands on the size of the species to be transported (the migration of large molecules across membranes has recently become known [103]). The main idea is that, at least in some cases, no real penetration takes place *through* the membrane, which is a one-sided surface. We suppose that a particle Z is firmly attached to a site on the "outside" of the membrane (Fig. 3*a*). If a change in the conformation of the surface is now induced by this bonding or some other cause, the site may move "inside" (Fig. 3*b*), where the particle is removed from the membrane. Thus the apparent result is the penetration of Z through the membrane¶, which is actually a consequence of the conformational change in the surface—a special kind of allosteric effect.

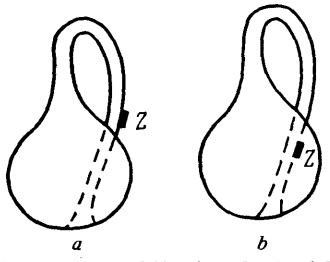


Figure 3. Illustration of the topological hypothesis of membrane transport.

The energy relations observed in membrane transport may be an indication of the energetics of this conformational change. Certain consequences can be deduced from the suggested model: (1) substances that change the permeability of membranes should exert an allosteric action and/or combine selectively with certain molecules or ions; (2) certain molecules known as good complexing agents will not, however, increase appreciably the permeability of membranes for the corresponding ions, owing to the absence of an allosteric effect; and (3) strong effectors will accelerate non-selectively the transport of various species owing to the enhanced conformational lability of the membrane. The specific chemical mechanisms of bonding both effectors and transportable species with the membranes can obviously be extremely varied. The separation of allosteric and complexing effects may assist a better understanding of the problem.

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¶Simple penetration of molecules through channels connecting "internal" and "external" regions may be prevented by the size of these channels.

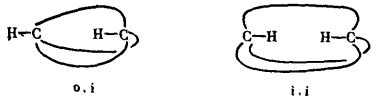
In the Reviewer's opinion structural topology is one of the growth points of modern stereochemistry. The technical difficulty of synthesising model compounds has hitherto been a strong restraining factor. The difficulties will probably diminish considerably during the next few years, after which rapid developments in this field must be expected, especially in the investigation of the chirality of topologically isomeric molecules. Without depending on the rate of experimental development, ideas arising from topology play an important part in the complex of concepts involved in modern stereochemistry.

ADDENDUM

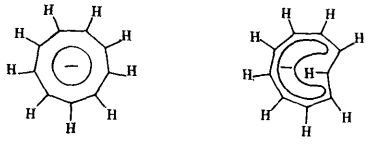
The ideas forming the subject of this Review have been further examined in several recent papers.

Schill et al. [104] have continued their directed synthesis of a catenane (Scheme 3), passing to a simpler compound by ozonolysis of the aromatic ring followed by reduction of the carbonyl groups to methylene. In this way they have obtained the ancestral [28, aza-25]catenane.

Park and Simmons [105] have extended their investigations of the conformational isomerism of macrobicyclic compounds, begun on diamines [86], to purely carbon systems. They have selectively synthesised i,i- and o,i-bicyclo-[8,8,8]hexacosanes



isomers whose structure is confirmed by the carbon-13 nuclear magnetic resonance spectra. Interconversion of the isomers has not yet been reported. A similar system, in which a hydrogen atom attached to a bridgehead carbon faces the interior of a rigid bicyclic molecule, has been prepared by Gassman and Thummel [106]. In this connection it is interesting that isomerism associated with the convexity or concavity of a planar polygon has already been observed [117] in the cyclononatetraenide anion



Research on cryptates is being vigorously pursued, both in the synthesis of new multidentate macrocyclic ligands and in their use for preparative purposes [107-111].

No weakening of interest is apparent in the preparation of polyhedra and other three-dimensional molecules, especially of the cluster type [112-115]. The trideca-atomic polyhedron of the carborane class is probably not convex [116].

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